

REMARKS

Applicants have carefully reviewed and considered the 11/23/07 Office Action and offer the following remarks. Applicants further acknowledge that the earlier 35 USC 112 rejection of claims 15 and 19 are withdrawn.

Currently claim 19 has been amended; claims 3, 5-6, 8-9, 11 and 18 have been canceled; as a result, claims 1-2, 4, 7, 10, 12-17 and 19 are now pending in this application.

§112, Second Paragraph Rejection

Claim 19 was rejected under 35 USC § 112, second paragraph, as containing subject matter which was not particularly point out and distinctly claimed because there was no antecedent basis for "the cells concomitantly administered with the hNT cells." Applicants have amended claim 19 to overcome that rejection and respectfully request reconsideration and withdrawal of this ground for rejection.

§ 103 Rejection of the Claims

Claims 1-2, 4 and 17 were rejected under 35 USC § 103(a) as being unpatentable over the Weiss patent (U.S. 5,851,832 - the '832 patent) in view of Sanberg et al. (Abstract 1997) and further in view of Grabowski et al. (1994) as set forth at pages 3-5 of the office action.

The Office Action stated that the '832 patent discloses treatment of neurodegenerative disease (specifically Parkinson's Disease), stroke and brain injuries with stem cells. Moreover, Weiss teaches administration of neural stem cell progeny to mice and rats by administering up to 50×10^6 cells per ml. The Office Action states that Sanberg et al used about 30,000 hNT cells per rat. The Office Action also stated that Grabowski taught grafting fetal cortex cells at 5 days, and 3 or 5 weeks. The Office Action concludes that combining the teachings of Weiss (treating stroke in humans with neural cells), of Sanberg (administering hNT cells, which if ramped up to human-size recipients, would have been about 10 million hNT cells), and of Grabowski (achieving more success at 8 weeks than 5-7 days postsurgical) would have met all the claimed elements if one assumes that it would have been obvious "to minimize inflammatory trauma at any one site [by delivering] the cells to multiple injured brain regions." (page 5)

First, to establish a *prima facie* case of obviousness under 35 U.S.C. §103, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the cited prior art references must teach or suggest all of the claim limitations. Furthermore, the suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not based upon the Applicants' disclosure. A failure to meet any one of these criteria is a failure to establish a *prima facie* case of obviousness. MPEP §2143. Furthermore, a rejection must deal with the Graham factors, including long-felt need and the failure of others. We do not believe that these latter factors in particular were appreciated by the Office.

Let us start by reviewing the invention and claims under consideration. The Applicants are the first known inventors to inject hNT neuronal cells into humans for the treatment of stroke (subsequent to an arduous preclinical process and filing of an IND). The treatment method includes delivering 2 or 6 million viable hNT neuronal cells to a plurality of brain sites involved in the stroke. The Applicants then followed the patients for a number of months. Only when the patients were evaluable and showed improvement did the Applicants file the instant patent application. The results obtained show that administration of at least six million viable neuronal cells is unexpectedly superior to delivery of two million cells in treating humans with conditions such a stroke, Parkinson's disease, Huntington's disease or trauma which involve brain damage or degeneration.

As indicated in the present application at page 15, measurement of the ESS (European Stroke Scale) in patients showed that after six months the mean change from base line was 1.8 points in the patients given two million viable neuronal cells, indicating no noticeable clinical benefit. However, when the patients were given six million viable neuronal cells, their scores were much higher at 5.3 points, resulting in a clinical benefit. Thus, the application as filed shows a clear benefit in the use of at least six million viable neuronal cells.

The improved results following transfer of at least six million viable neuronal cells are also seen in the motor elements of ESS indicated at page 16, first full paragraph of the present application. After six months, the mean change from base-line was only 1.9 points for the two

million viable cell group, but double that (3.8 points) for the six million viable cell group. As indicated at page 17, first paragraph, the transfer of six million viable neuronal cells also did not cause the rise in systolic blood pressure seen with the transfer of only two million cells.

Thus, as concluded at page 17, final paragraph, of the present application:

"the stroke scale results suggest that the cells may be efficacious and that the higher dose administered may be more efficacious than the lower dose."
(emphasis added)

As indicated on pages 9 to 12 of the instant application, ESS, BI and SF-36 are measures of ability to perform standard life activities, general health and the remaining impact of a stroke. Thus, the improvements seen with six million viable cells are important for improving the ability of victims of stroke to cope with normal life and display recovery.

As stated above, to satisfy the Section 103 requirement of reasonable expectation of success, we need to look at the state of the art at the date of the application filing. The state of the art for treating humans with stroke in 1999 was dismal, with no significant expectation of success. Rather than being predictable, history shows the failure of others to attain Applicants' achievement. "The failure to translate the positive effects of a variety of neuroprotective strategies [for stroke] from animal models to human trials has perplexed investigators." (Davis and Donnan, 2001, Stroke 33:309-10) This is important because even THREE YEARS after the 1999 filing date, others still failed to attain Applicants' achievement.

Dr. Wechsler's declaration (attached) includes more proof that animal results were NOT translated to humans at the time of the filing of the patent application and even later.

Previously Applicants modified the claims to recite the treatment of stroke in humans using at least 6,000,000 viable hNT cells. Since others have failed to successfully treat chronic stroke in humans, treatment with hNT cells is novel and nonobvious. The following discusses the references in the light of the current claims.

Viewing the Weiss '832 reference as a whole, one can see that both rodent (Examples 1-8) and primate cells were processed to produce neurospheres and their progenies, including nerve cells and other nervous tissue cells. In addition, some rodent models were implanted with either embryonic or adult-derived nervous tissue. Moreover, there is a hypothetical example of a "patient" with unspecified "neurodegenerative disease" receiving fetal cells (Example 14).

Examples 16 and 17 also are hypothetical examples of the treatment of the demyelinating diseases. Example 18 is a hypothetical example of administration into a human patient in the method described in Example 14. Given the state of the art in 1999 (and earlier in 1995 when this CIP was filed), these hypothetical examples are merely evidence of a *long-felt need* to treat brain disorders in humans. The Office Action alleges that Weiss used the same method as mentioned on page 5 of the instant specification and characterized the specification mention as “support” for the instant claims. However, page 5 is part of the BACKGROUND and was merely mentioned as prior art, which is similar to that found by the Office. The support for the claims is in the instant specification’s description of the successful treatment of human patients, accomplishment of a *long-felt need*. Moreover, Weiss did not administer the claimed cells, did not administer cells in claimed multiple locations, did not administer a minimum number of viable cells, and did not administer cells to humans with strokes at least 3 hours earlier. For these reasons, the Applicants believe that Weiss does not support the stated reasons for rejection.

Similarly, the Sanberg et al teachings are based on the implantation of hNT cells in an animal model and do not even provide a hypothetical human example, so the teachings merely represent a *long-felt need*. Moreover, Sanberg et al teachings do not disclose other important limitations in the claims, including the number of cells appropriate for human use or a requirement to provide a minimum number of viable cells.

The third reference is Grabowski et al disclosing a rodent model and an unclaimed source of cells. While Grabowski suggests that longer delay in administering the cells (as long as 3 months), there is no experimental support for that proposal. Therefore, the mere presence of an unsupported allegation does not render obvious the claimed invention. Moreover, because Applicants describe in the specification the first successful use in humans in time frames of 6 months to 6 years post-stroke, Applicants have enabled the instant claims. Grabowski does not disclose the following claimed elements: use of hNT cells, a minimum number of viable cells, administration to a plurality of sites, or use in humans.

The Office Action called dosing cells for stroke in humans obvious. The Office Action also stated that one of ordinary skill in the art would make multiple injections in the brain to reduce the inflammatory trauma at any one site. In response, the Examiner is invited to review Dr. Wechsler’s declaration which is attached. Therein, Dr. Wechsler states in paragraph 9 that it

is not sufficient to scale up dose on the basis of quantity per kilogram and that others have said that neuroprotective drug dose ranges and toxicities in animals may not overlap with those tolerated in humans. Besides, simple multiplication of Dr. Sanberg's optimal dose would result in 10 million cells, which is almost twice as much as benefited patients in the instant study. Thus, the claimed dosing would not have been obvious. As for the multiple injection in the brain reducing inflammatory trauma at any one site, Dr. Wechsler noted that having a greater number of separate sites could actually increase the chance of at least one site becoming infected. Because the specification indicates that no patients showed inflammation, the allegation of obviousness appears to be hindsight based on reading of the specification and the later articles published by the Applicants. Therefore, these two claimed elements (dose and multiple injections) were not obvious before the Applicants demonstrated them. Also it is not clear how dosing or non inflammation could be obvious when the prior art demonstrated complete *lack of success* in administering drugs and cells for brain disorders that were successful in rodents to humans (see paragraphs 2, 5, 5 and 7).

Because the combination of references fails to teach every limitation of the instant claims 1-4, and supplying the missing elements is not obvious to one skilled in the art, this ground for rejection appears to be moot. Applicants respectfully request that it be withdrawn.

Next, the Office Action issued a Section 103 Rejection of claims 7-19, over Sanberg and Weiss, in view of Uchida (1995).

The Office Action states that Sanberg reported cognitive function in rats transplanted with hNT cells or striatal cells. The Applicants believe that these proofs are limited to the conclusion that in rodent models for stroke, hNT cells have proven successful. There is no report of use in humans, administration of at least 6 million cells or sterile conditions. The Office Action also stated that Sanberg teaches treating animals with sensory and motor damage from stroke, but Applicants could not find that teaching.

Weiss was discussed above. Weiss fails to teach successful use if hNT cells in humans. Lack of any successful use in ANY human condition undercuts the allegation of support for treatment neurodegenerative diseases, brain injury, other CNS dysfunctions or demyelinating diseases. The Office Action proposed that sterility of the cell composition would be expected; however, most sterilization techniques damage or kill cells, so sterility is certainly not a given if

one wants to maximize the yield of viable cells. Just using a sterile solution control and sterile collection apparatus are insufficient to assure sterility of the cellular composition. The Office Action states that Weiss can be read to support the administration of 38 million cells to humans, but that is not even close to the 6 million claimed. Applicants agree that Weiss did not administer cells into the cisternae as recited in claim 16 or into a plurality of brain sites as recited in claim 7, 13, 14, 15 and 17.

The Office Action next notes that Uchida et al now is relied up for the motivation of selecting additional cell types that are available in the embryonic neural plate, when in a prior Office Action this reference was not relied upon for teaching which type of cell to implant. Uchida is cited to prove that transplanted cells have the capacity to migrate to distant sites. The Office Action goes on to state that co-administration of "two treatments known to be effective for the same purpose" would be obvious. Given that NO prior treatments of stroke in humans have been successful, co-administration of any treatment would be expected to be unsuccessful and would therefore be unobvious. Similarly, treating motor disorders in rodents has no predictive power for treating motor disorders, speech, etc. in humans. As the Applicants have previously noted, Uchida et al are equivocal about the possibility that their embryonic cells migrate; therefore, there is no teaching that would support a rejection for hNT cells migrating. As previously noted, the Uchida reference states that "[i]t cannot be ruled out that the 'distant' cells were *deposited at their sites during implantation* (emphasis added)." Therefore, the teachings of Uchida are inconsistent and cannot be used to support the use of Uchida for the proposition that ALL transplanted cells can migrate to distant sites. Because no method of treating stroke that was successful in rodents had been successful in humans at the filing date of the instant application, no method of treatment could be obvious, including intracisternal injection.

Taking all the references together, none teach the use of hNT cells to treat stroke in humans, nor do they teach or suggest the recited dosage. Successful rodent tests of stroke did NOT result in success in humans until Applicants were successful.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (480-344-7745) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3956.

Respectfully submitted,

By their Representatives,

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